VI. DEVELOPMENT OF STANDARD

Basis for Previous Standards

Federal occupational standards presently exist for two of the selected nitriles, namely, acetonitrile and tetramethylsuccinonitrile. Both standards are based on the threshold limit values (TLV's) for workplace exposure previously adopted by the American Conference of Governmental Industrial Hygienists (ACGIH).

In 1960, the ACGIH proposed a tentative limit of 40 ppm (70 mg/cu m) for acetonitrile [111], and this limit was adopted in 1962 [112]. The proposed limit was based on an accidental group exposure reported by Grabois [31] and Amdur [32], and on human and animal studies conducted by Pozzani et al [35].

Grabois [31] reported an incident in which 16 chemical workers were accidently exposed to acetonitrile vapor while painting the inside walls of a storage tank. Acetonitrile was used as a thinner for the corrosion-resistant resinous paint. The workers became ill during the 2nd day of exposure, after the paint was warmed to facilitate application and ventilation was interrupted. One worker died, two were seriously ill when hospitalized, and eight others later were admitted to a hospital.

In a more detailed description of the same incident, Amdur [32] reported that the onset of illness was delayed 3-12 hours after exposure. The author attributed the toxicity to slow metabolic release of cyanide ions from acetonitrile. When ventilation was restored and the paint was used at room temperature, no incidents were observed at organic cyanide concentrations of 17 ppm or less.

Pozzani et al [35] exposed three subjects to acetonitrile vapor at 40 ppm for 4 hours, and two subjects were similarly exposed at 80 ppm and 160 ppm. One of the three subjects exposed at 40 ppm described a slight tightness of the chest and a "cooling sensation" in the lungs, similar to that produced by inhaling menthol, and he had increased thiocyanate concentrations in the urine. One of the two subjects exposed at 160 ppm had a slight flushing of the face after exposure, followed by a feeling of bronchial tightness.

Pozzani et al [35] suggested a standard of 40 ppm for acetonitrile on the basis of the 20-ppm standard for acrylonitrile set in 1942. This was supported by animal studies that showed that acetonitrile vapor had only a fraction of the toxicity of acrylonitrile but that both released cyanide in vivo and produced a varied species response. A standard of 40 ppm for acetonitrile was considered safe because it was shown to be less toxic than

acrylonitrile in rats, dogs, and monkeys. In 1959, the authors stated that "because of the above considerations and the fact that the permissible acrylonitrile concentration figure has withstood the test of time, it is reasonable to suggest an initial hygienic standard for acetonitrile vapor of no more than 40 ppm. This may be modified by human experience as data on acceptability and clinical evidence of safety are accumulated."

In 1965, the ACGIH proposed a tentative limit of 0.5 ppm (3 mg/cu m) for tetramethylsuccinonitrile [113], and this limit was adopted in 1967 [114]. This limit was intended to prevent systemic effects experienced by workers [115]. The recommended limit was based in part on the experience of workers in Europe who had headache, nausea, convulsions, and coma after working with vinyl foam or vinyl products [43], and was supported by the toxic effects observed in animals exposed to tetramethylsuccinonitrile [43,77]. The 1967 ACGIH listing [114] included the notation "skin" along with the recommended TLV, indicating that percutaneous absorption of tetramethylsuccinonitrile must be prevented if the limit is to protect employees from the toxic effects of exposure to the compound.

The current Federal occupational standards (ie, air contaminant limits) for acetonitrile and tetramethylsuccinonitrile were adopted from the 1968 ACGIH TLV listing by the Occupational Safety and Health Administration (OSHA) in 1971, under the provision of the Occupational Safety and Health Act of 1970. The standard for workplace exposure to acetonitrile is an 8-hour TWA concentration limit of 70 mg/cu m (40 ppm) and that for tetramethylsuccinonitrile is an 8-hour TWA concentration limit of 3 mg/cu m (0.5 ppm) with a "skin" notation. NIOSH/OSHA Draft Technical Standards have been developed as part of the Standards Completion Program to augment the current Federal limits for acetonitrile and tetramethylsuccinonitrile.

Permissible exposure levels have been established by foreign countries for four of the selected nitriles [116]. With respect to acetonitrile, Australia, Belgium, the Federal Republic of Germany, Finland, the Netherlands, Switzerland, and Yugoslavia established levels at 70 mg/cu m (40 ppm) determined as an 8-hour TWA, the USSR set a maximum allowable concentration (MAC) of 10 mg/cu m (6 ppm), and Rumania set an MAC of 50 mg/cu m (29 ppm) and an average concentration limit of 30 mg/cu m (18 ppm) with a "skin" notation. For acetone cyanohydrin, Hungary and the USSR established MAC levels of 0.9 mg/cu m (0.3 ppm). Italy set an 8-hour TWA limit of 70 mg/cu m (20 ppm), and Rumania established a TWA limit of 15 mg/cu m (4 ppm) and an MAC at 25 mg/cu m (7 ppm). Both the USSR and Rumania warned of possible skin absorption. With respect to adiponitrile, the USSR and Yugoslavia set MAC levels of 20 mg/cu m (5 ppm). With respect to tetramethylsuccinonitrile, Australia, Belgium, the Federal Republic of Germany, Finland, the Netherlands, and Switzerland established levels of 3 mg/cu m (0.5 ppm) determined as an 8-hour TWA. All but Australia and Switzerland had a "skin" notation in addition to the listed value.

Basis for the Recommended Standard

In general, acute exposure of humans to the selected nitriles can cause headache, dizziness, vomiting, profuse sweating, loss of consciousness, convulsions, coma, and death [2,10,31,32]. Autopsy findings in humans overexposed to acetonitrile indicate a general distribution in body tissues of acetonitrile and hydrogen cyanide, both free and combined [10,33]. The reported toxic effects after exposure to the selected nitriles resemble the toxic effects of cyanide [2,10,31,32]. Although cyanide is well known as an acute and fast-acting poison [88], the signs and symptoms of nitrile poisoning are characterized by a delayed onset generally attributed to the time required for metabolic release of cyanide [26-28,40,42,63]. Cyanide acts by inhibiting cytochrome oxidase and thus impairs cellular respiration [42]. At higher concentrations, cyanide may completely inhibit cellular respiration and produce histotoxic anoxia [117]. Evidence for the cyanide effect of various nitriles is supported further by the reported effectiveness of specific cyanide antidotes, such as sodium nitrite and sodium thiosulfate, in the treatment of acute overexposure [2,10,16].

A review of the human and animal toxicity information presented in Chapter III reveals that sufficient quantitative inhalation toxicity data needed for recommending workplace exposure limits for nitriles are available only for acetonitrile. Comparison of toxicity, therefore, is made with acetonitrile, either directly or indirectly, in developing the recommended standard for other nitriles.

The toxicity ratios of various nitriles injected by the sc route of administration in female rats are presented in Table VI-1. The LD_{50} values submitted by S Szabo (written communication, May 1978) are approximated values; however, the advantages of using these values for comparative toxicities of various nitriles are that these values were obtained by the same route of administration (sc), in the same species (rats), and in the same sex (female). The strain (CD rats) and weight (200 g) of the animals used were also comparable.

The LD_{50} values reported by Szabo are within the same range as those reported by other investigators using different parenteral routes of administration. Tsurumi and Kawada [64] reported an LD_{50} value of 0.25 ml/kg (193 mg/kg) for isobutyronitrile in ip-injected Wistar-strain female rats (130-150 g). The LD_{50} value reported by Szabo for isobutyronitrile injected sc was 300 mg/kg. Macht [73] reported an LD_{50} value of 250 mg/kg for succinonitrile in iv-injected rats, whereas Szabo reported an LD_{50} value of 250 mg/kg for succinonitrile in rats injected sc. However, the major difficulty in ranking this group of nitriles on the basis of relative toxicities from these data is that the few values obtained on relative toxicities by inhalation (Table VI-2) do not agree closely with those obtained by sc injection. For example, Table VI-1 indicates that n-butyronitrile is 1.5 times as toxic as isobutyronitrile in rats by sc injection. However, both of these nitriles had minimal lethal

TABLE VI-1

TOXICITY RATIOS OF VARIOUS NITRILES INJECTED SUBCUTANEOUSLY IN FEMALE RATS

Nitrile	LD_{50} (mg/kg)	LD_{50} (millimole/kg)	Molar LD_{50} Ratio with Respect to Isobutyronitrile
Isobutyronitrile	300	4.34	1.00
Propionitrile	150	2.72	1.60
n-Butyronitrile	200	2.89	1.50
Malononitrile	100	1.51	2.87
Adiponitrile	200	2.12	2.05
Succinonitrile	250	3.12	1.39

Adapted from S Szabo, written communication, May 1978

TABLE VI-2

MINIMUM LETHAL CONCENTRATIONS FOR RATS EXPOSED TO SELECTED NITRILES BY INHALATION*

Nitrile	Calculated MLC (mg/cu m)
Acetonitrile	3,857
Propionitrile	1,134
n-Butyronitrile	1,619
Isobutyronitrile	1,619
Tetramethyl-succinonitrile	235
Glycolonitrile	350
Acetone cyanohydrin	211

*The MLC is the lowest concentration that kills at least one rat when a group of rats is exposed to the airborne nitrile for 4 hours.

Adapted from references 79-83

concentrations for the rat during a 4-hour exposure of 1,619 mg/cu m [81,82]. Propionitrile is 1.6 times as toxic as isobutyronitrile by sc injection (Table VI-1), but 1.4 times as toxic by inhalation in the same species (Table VI-2). Although these three nitriles are the only ones among those studied by Szabo for which inhalation toxicities are apparently available, the difference between the relative toxicities of these compounds by these two routes of administration indicates that the workplace environmental concentration limits for the nitriles should be based on relative toxicities by inhalation when such data are available.

Table VI-3 relates the toxicities of other selected nitriles to those of acetonitrile by several routes of administration. The ratios indicate that the agreement between the comparative toxicities by different routes is poor in some cases.

On the basis of these figures, propionitrile is 3.4 times as toxic by inhalation as acetonitrile; n-butyronitrile and isobutyronitrile are 2.4 times as toxic; tetramethylsuccinonitrile is 16.5 times as toxic; glycolonitrile is 11.0 times as toxic; and acetone cyanohydrin is 18.3 times as toxic.

The toxicities of propionitrile, n-butyronitrile, isobutyronitrile, tetramethylsuccinonitrile, glycolonitrile, and acetone cyanohydrin have been related to that of acetonitrile because of the comparatively extensive information about the toxic properties of this nitrile. Since a similar basis of comparison by inhalation exposure does not exist for the remaining nitriles, the molar LD_{50} ratios for the subcutaneously administered nitriles presented in Table VI-1 are the primary basis for developing recommended workplace environmental limits for malononitrile, adiponitrile, and succinonitrile.

(1) Mononitriles

Acetonitrile, propionitrile, n-butyronitrile, and isobutyronitrile show similar toxic effects in animals [2,10,35]. These compounds may be inhaled, absorbed through the skin, or ingested. Acute toxic effects observed in animals include labored breathing, anuria, ataxia, cyanosis, coma, and death. Tissue distribution studies indicate that mononitriles are distributed uniformly in various organs [33,53] and that cyanide metabolites are found predominantly in the spleen, stomach, and skin, with smaller amounts present in the liver, lungs, kidneys, heart, brain, muscle, intestines, and testes [53]. Acetonitrile [54] and other mononitriles [36,37] are excreted partly unchanged in the urine or in exhaled air.

(A) Acetonitrile (1 ppm = 1.7 mg/cu m)

McKee et al [38] and Dalhamn et al [36,37] demonstrated that acetonitrile can be absorbed by oral tissues, retained by the lungs, and partly excreted unchanged in the urine of cigarette smokers.

TABLE VI-3

COMPARATIVE TOXICITIES OF ACETONITRILE AND OTHER SELECTED NITRILES

	Inhalation MLC (Rats)	Dermal LD_{50} (Rabbits)	Intraperitoneal LD_{50} (Mice)	Oral LD_{50} (Rats)
Acetonitrile/ Propionitrile	3.4	6.0	15.5	64.3
Acetonitrile/ n-Butyronitrile	2.4	2.5	11.4	18.5
Acetonitrile/ Isobutyronitrile	2.4	4.0	-	24.6
Acetonitrile/ Malononitrile	-	-	40.1	41.1
Acetonitrile/ Adiponitrile	-	-	13.0	8.4
Acetonitrile/ Tetramethyl-succinonitrile	16.5	-	-	100.3
Acetonitrile/ Glyconitrile	11.0	250.0	-	156.7
Acetonitrile/ Acetone cyanohydrin	18.3	73.5	62.0	147.2

Adapted from references 79-85,118-120

Amdur [32] and Grabois [31] described an accidental exposure to acetonitrile vapor in which 16 workers were exposed to acetonitrile at unknown concentrations for up to 12 hours. Nine of these workers who became ill reported symptoms of fatigue, nausea, chest pain, and headache and showed signs of hypothermia, hypotension, oliguria, coma, absence of deep reflexes, skin discoloration, and respiratory irregularities. One of the workers died within 24 hours of exposure.

Pozzani et al [35], in experiments with humans, found that one of three subjects, after inhaling acetonitrile at 40 ppm for 4 hours, experienced tightness of the chest that persisted for 24 hours. This subject also showed a slight increase in urinary thiocyanate concentration. Although these minimal effects were present in the youngest (age 31) of the three subjects, the other two showed no effects. Another subject exposed at 160 ppm experienced a slight flushing of the face and tightness of the chest after exposure but did not show significant changes in blood cyanide or urinary thiocyanate concentrations.

Pozzani et al [35] also studied the effects of inhaling acetonitrile on rats, dogs, and monkeys. Animals were exposed at 166-2,510 ppm acetonitrile 7 hours/day for up to 13 weeks (5 days/week). One monkey exposed at 2,510 ppm died on the 2nd day of exposure; two monkeys exposed at 660 ppm died in 23 and 51 days, respectively; and one monkey exposed at 330 ppm survived the duration of exposure. Monkeys exposed at 660 ppm showed poor coordination during the 2nd week of exposure, and the monkey exposed at 330 ppm showed hyperexcitability toward the end of the 13th week. Dogs exposed to acetonitrile at 350 ppm for 7 hours/day for 13 weeks (5 days/week) showed decreases in body weight and hemoglobin and hematocrit values.

Pozzani et al [35] reported LD_{50} values of 0.85 and 0.95 ml/kg (calculated from the author's data to be 707 mg/kg from a mean of 0.90 ml/kg) in female rats administered acetonitrile ip. Rats exposed to acetonitrile at 655 ppm for 7 hours/day, 5 days/week, for 13 weeks, had significant microscopic changes involving the kidneys, liver, and lungs. There were reversible lesions of the lungs, such as alveolar capillary congestion and focal edema, often accompanied by bronchial inflammation, desquamation, and hypersecretion of mucus. Osmotic swelling of mitochondria in tubular epithelial cells of the kidneys and in hepatocytes in the central portion of hepatic cords was also seen. Three of the 26 rats exposed at 330 ppm and 2 of the 28 exposed at 166 ppm for 13 weeks showed tissue abnormalities in the lungs.

In summary, exposure of humans to acetonitrile at 40 ppm for 4 hours [35] produced slight chest tightness in one of three experimental subjects. Amdur [32], in describing an incident of acute effects from exposure of workers to acetonitrile at high concentrations, commented that after controls that lowered the exposure to 17 ppm were instituted there were no

further complaints. Thus, it appears that exposure to acetonitrile at 40 ppm produced minimal effects, whereas no observable effects were produced in humans at 17 ppm. Therefore, NIOSH recommends that the current Federal standard of 40 ppm for acetonitrile be reduced to 20 ppm (33.6 mg/cu m) as a TWA limit for up to a 10-hour workshift in a 40-hour workweek.

(B) Propionitrile (1 ppm = 2.3 mg/cu m)

No human toxicity data were found for propionitrile. In animal studies, the prominent effect of propionitrile is the formation of duodenal ulcers in rats [56-61]. All these studies utilized the sc route of administration.

Comparison of the inhaled minimal lethal concentrations in Table VI-2 for propionitrile and acetonitrile shows that propionitrile was about 3.4 times as toxic as acetonitrile by this route of administration. On this basis, NIOSH recommends that employee exposure to propionitrile not exceed 6 ppm (14 mg/cu m) as a TWA concentration for up to a 10-hour workshift in a 40-hour workweek.

(C) n-Butyronitrile (1 ppm = 2.8 mg/cu m)

No human toxicity data were found for n-butyronitrile. Using sc administration in rats, Szabo and Reynolds [62] observed that n-butyronitrile had higher ulcerogenic and adrenocorticolytic potency than propionitrile. Haguenoer and Dequidt [63] found that the lethal dose for male rats by ip injection was about 150 mg/kg, whereas at 100 mg/kg only two of six rats died in 8 days.

According to the data presented in Table VI-2, inhaled n-butyronitrile is about 2.4 times as toxic as acetonitrile in rats. Thus, reduction of the TWA limit recommended for acetonitrile by this factor appears to be adequate to protect the heatlh of workers exposed to n-butyronitrile. NIOSH therefore recommends that employee exposure to n-butyronitrile not exceed 8 ppm (22 mg/cu m) as a TWA limit for up to a 10-hour workshift in a 40-hour workweek.

(D) Isobutyronitrile (1 ppm = 2.8 mg/cu m)

Zeller et al [10] and Thiess and Hey [39] reported three cases of inhalation exposure to isobutyronitrile. Symptoms of all three appeared 10-60 minutes after exposure. One worker was exposed at an unknown concentration for 10 minutes and reported dizziness and vomiting; he became unconscious and experienced circulatory collapse. He also had convulsions but recovered in a few days. The other two workers, also exposed at unknown concentrations, reported headache, dizziness, and vomiting. No other human toxicity data were found for isobutyronitrile.

The inhalation toxicity data for isobutyronitrile in mice and rats suggest that this chemical is rapidly toxic in both species [64]. All mice and rats died within 24 hours when exposed for 2 and 10 minutes, respectively, to atmospheres nominally saturated with isobutyronitrile. A significant number of deaths also occurred in both mice and rats when similarly exposed for 30 seconds and 6 minutes, respectively.

Isobutyronitrile has also been toxic by other routes of administration [64]. The lethal dose of isobutyronitrile administered to mice ip was less than 50 µl/kg (38 mg/kg), indicating a high toxicity for this species. The LD_{50} for female rats injected ip was calculated as 0.25 ml/kg (193 mg/kg).

In a subchronic study, no remarkable signs of toxicity, including deaths, occurred when male and female rats were injected ip with isobutyronitrile once daily for 14 days at 30 or 50 µl/kg or were administered 0.2 ml/kg orally. The only significant change observed was the parenchymatous degeneration of the liver in rats receiving 50 µl/kg. Male rats showed a greater degree of liver cell degeneration than did females.

According to the inhalation data presented in Table VI-2, the acute toxicity of isobutyronitrile appears to be about 2.4 times that of acetonitrile. NIOSH therefore recommends that employee exposure to isobutyronitrile not exceed 8 ppm (22 mg/cu m) as a TWA limit for up to a 10-hour workshift in a 40-hour workweek.

(2) Cyanohydrins

The principal route of exposure to cyanohydrins appears to be dermal [2,39,42], but these nitriles can also be inhaled. Because of the alpha-hydroxy group, these compounds will dissociate readily to yield hydrogen cyanide and the corresponding aldehyde or ketone [2]. The onset of toxicity is related to the time required for dissociation to produce free hydrogen cyanide.

Shkodich [65] reported that the stability of acetone cyanohydrin in solution was pH dependent, with stability being greater in an acid medium. Thus, at pH 7.4, alpha-cyanohydrins may spontaneously release cyanide ions. The rapid onset of toxicity further supports the ready release of cyanide ion from cyanohydrins.

(A) Acetone Cyanohydrin (1 ppm = 3.5 mg/cu m)

Sunderman and Kincaid [2] reported a case of exposure to acetone cyanohydrin in which a worker had skin exposure from a splash of the compound. He had symptoms of nausea 3 hours after exposure, lost consciousness, convulsed, and died 6.5 hours after exposure. The authors

also described three nonfatal cases involving operators who had dermal exposure to acetone cyanohydrin while packing pumps leading to and from storage tanks. The workers lost consciousness but revived after they were carried into fresh air and their hands were washed.

Krefft [41] reported two incidents of acute exposure involving fatalities that resulted from accidental spilling and splashing of acetone cyanohydrin on the face and clothing of workers. Other cases of acetone cyanohydrin intoxication have been reported [10,39,42]; however, no quantitative data for humans are available to enable correlation of exposure concentration with effect.

Shkodich [65] reported LD_{50} values in four animal species administered acetone cyanohydrin by an unspecified route. The mice showed the highest sensitivity to acetone cyanohydrin with an LD_{50} value of 2.9 mg/kg. The LD_{50} values for the other animals were: albino rats, 13.3 mg/kg; guinea pigs, 9 mg/kg; and rabbits, 13.5 mg/kg. Sunderman and Kincaid [2] reported an LD_{50} value of 120 mg/kg in albino guinea pigs by the dermal route. They also reported that 50% of rats died within approximately 10 minutes after exposure to saturated, purified acetone cyanohydrin vapor. These LD_{50} values suggest that acetone cyanohydrin is highly toxic in animals.

Motoc and associates [66] reported that acetone cyanohydrin administered orally to white rats (5 mg, twice a week for 3, 5, or 8 months) and by inhalation (1 ml in 84 liters of air, twice a week for 3, 5, or 8 months) caused serious liver and kidney lesions that became irreversible with prolonged duration of exposure. Inhalation of acetone cyanohydrin also produced lung damage. These lesions were degenerative with desquamation of bronchial epithelium progressing to superficial ulceration.

Because the data in Table VI-2 indicate that acetone cyanohydrin is about 18.3 times as toxic as acetonitrile by inhalation and because the alpha-cyanohydrins seem to dissociate readily to release hydrogen cyanide [2], NIOSH recommends a ceiling concentration limit no greater than 1 ppm (4 mg/cu m) for any 15-minute period for acetone cyanohydrin.

(B) Glycolonitrile (1 ppm = 2.3 mg/cu m)

Wolfsie [40] described two cases of human skin exposure to unknown quantities of 70% aqueous solution of glycolonitrile. Both workers experienced symptoms of headache, dizziness, unsteady gait, and general weakness within 1 hour after leaving work. They later experienced vertigo, respiratory distress, retching, and loss of appetite. The two workers initially recovered in 1 day, but feelings of nausea and weakness returned and persisted for 5 days in one worker. No other human toxicity data are available for glycolonitrile.

Wolfsie [40] also reported that six of seven mice, two of seven rats, and none of seven guinea pigs died when exposed to glycolonitrile at 27 ppm for 8 hours. The remaining mouse and four additional rats died within the next 18 hours.

In another study, Wolfsie [40] reported an oral LD_{50} of 10 mg/kg for male albino mice and a dermal LD_{50} value between 105 and 130 mg/kg for albino rabbits. These data indicate that glycolonitrile is significantly more hazardous than acetonitrile. As shown in Table VI-2, glycolonitrile was about 11 times as toxic to rats as acetonitrile by the inhalation route. A reduction of the limit recommended for acetonitrile by this factor, therefore, appears to be adequate to protect the health of workers exposed to glycolonitrile. However, because of the expected rapid onset of toxic action, NIOSH recommends that the occupational exposure limit for glycolonitrile not exceed a ceiling concentration of 2 ppm (5 mg/cu m) for any 15-minute period.

(3) Dinitriles

The effects of exposure to the selected dinitriles--malononitrile, adiponitrile, succinonitrile, and tetramethylsuccinonitrile--are similar. Effects on the respiratory, circulatory, and central nervous systems were observed after iv administration of malononitrile in humans [121,126-128] and following ingestion of adiponitrile in animals [16]. Tetramethylsuccinonitrile produced respiratory and CNS effects in animals [77]. Dinitriles have also produced irritation of the skin and eyes [10,68].

Malononitrile and succinonitrile released cyanide in vivo and were ultimately excreted as thiocyanate in urine [16,74-76]. Stern et al [72] also demonstrated the formation of thiocyanate from malononitrile and thiosulfate by liver and kidney tissues in vitro. The release of cyanide from dinitriles suggests that the mechanism of acute toxicity of dinitriles may be similar to that of mononitriles.

(A) Malononitrile (1 ppm = 2.7 mg/cu m)

The only human toxicity data on malononitrile found are those reported during the clinical use of the compound in the treatment of various forms of mental illness [26,27,29]. The treatment consisted of repeated administration of malononitrile (1-6 mg/kg, 3-12 doses in 2-5 weeks). Signs and symptoms of toxicity included tachycardia, facial redness, headache, nausea, vomiting, shivering, cold hands and feet, muscle spasms, and convulsions.

Panov [68] reported that mice subjected to a single 2-hour inhalation exposure to malononitrile showed signs of restlessness, increased rate of respiration in the early posttreatment period followed by lassitude, decrease in respiration rate, cyanosis, incoordination of movements,

trembling, convulsions, and eventual death in some animals. The concentration of malononitrile to which the mice were exposed was not mentioned. The author also reported tearing, blepharospasm, hyperemia of the conjuctiva, and swelling of the eyelids after the direct application of liquefied malononitrile to the eyes of rabbits.

Panov [69] found that repeated exposure to malononitrile (3.6 mg/liter, 2 hours/day for 35 days) was only slightly toxic to rats, the principal result of such exposures being a slight anaplasia of red bone marrow evidenced by a slight decrease in the concentration of the hemoglobin in the blood and by reticulocytosis.

Hicks [71] reported that malononitrile induced brain lesions in rats. These were characterized by necrosis in the striatal neurons accompanied by proliferation of microglia and oligodendroglia 1-2 days after treatment. The author also observed demyelinating lesions of the optic tract and nerve, the cerebral cortex, the olfactory bulb, and the substantia nigra.

Studies indicate that malononitrile can produce CNS, respiratory, and cardiovascular effects in humans and animals [26,27,29,68,69,71]. However, no quantitative inhalation data are available from human or animal studies and, thus, the recommended standard is based on a toxicity ratio calculated in Table VI-1. The data indicate that malononitrile is about threefold as toxic as isobutyronitrile by the sc route of administration. NIOSH therefore recommends that employee exposure to malononitrile not exceed 3 ppm (8 mg/cu m) as a TWA limit for up to a 10-hour workshift in a 40-hour workweek.

(B) Adiponitrile (1 ppm = 4.4 mg/cu m)

While reviewing cases of adiponitrile poisoning that occurred in the occupational setting over a 15-year period, Zeller et al [10] reported that six of the seven cases that they encountered resulted in skin irritation and inflammation 5-15 minutes after exposure to adiponitrile. A seventh worker suffered extensive destruction of the skin of one foot after his shoe was drenched with adiponitrile.

The only other human case report found was that of an 18-year-old man who drank a few cc of adiponitrile while at work. About 20 minutes after ingestion, he experienced tightness in the chest, headache, profound weakness with difficulty in standing, and vertigo.

Ghiringhelli [16] estimated that 50 mg/kg of adiponitrile was the "lethal" dose for guinea pigs and reported that adiponitrile was metabolized to hydrocyanic acid and excreted in urine as thiocyanate. Svirbely and Floyd [78] reported that no adverse reproductive effects were observed for the first generation in rats exposed to adiponitrile at up to 500 ppm in drinking water.

Since no quantitative data for toxicity of adiponitrile by any route of exposure in humans or animals are available on which to base an occupational exposure limit, the limit must be based on the comparative toxicity of isobutyronitrile and adiponitrile in animals. The data presented in Table VI-1 suggest that adiponitrile is about twice as toxic as isobutyronitrile administered sc in female rats. NIOSH therefore recommends that employee exposure to adiponitrile not exceed 4 ppm (18 mg/cu m) as a TWA limit for up to a 10-hour workshift in a 40-hour workweek.

(C) Succinonitrile (1 ppm = 3.3 mg/cu m)

Animal data on succinonitrile include one LD_{50} study [73] and three pharmacokinetic studies [74-76]. The latter studies demonstrated that cyanide ions are released from succinonitrile and subsequently excreted as thiocyanate. Macht [73], during his LD_{50} study in mice, rats, and guinea pigs, observed signs of asphyxia and convulsions after administration of mean lethal doses of succinonitrile by various routes. During repeated dosing experiments, Macht found no impairment of hepatic and renal functions in rabbits and no effect on blood pressure in rabbits or cats.

Since no quantitative data from inhalation exposures of humans or animals necessary for recommending an occupational exposure limit are available, the workplace environmental limit is based on the comparative toxicity of isobutyronitrile and succinonitrile. The latter compound is about 1.4 times as toxic as the former. NIOSH therefore recommends that employee exposure to succinonitrile not exceed 6 ppm (20 mg/cu m) as a TWA limit for up to a 10-hour workshift.

(D) Tetramethylsuccinonitrile (1 ppm = 5.6 mg/cu m)

The only human toxicity report on tetramethylsuccinonitrile found in a search of the literature is that of Reinl [43]. His report covered a period of about 18 months at a single plant where employees used azo-isobutyronitrile as a propellant gas to produce polyvinyl chloride foam. The exposure to tetramethylsuccinonitrile was at an unknown concentration. The symptoms reported were headache or a sensation of pressure on the head, dizziness, nausea, vomiting, a peculiar taste and frothy spittle in the mouth, respiratory distress, insomnia, unconsciousness, and convulsions. All symptoms subsided after the installation of improved ventilation in the work areas.

In animal toxicity experiments, rats exposed at 6 ppm died after 30 hours of continuous exposure, and rats exposed at 60 ppm died after 2-3 hours of continuous exposure [77]. Harger and Hulpieu [77] reported that rats, guinea pigs, rabbits, and dogs treated with tetramethylsuccinonitrile

developed violent convulsions and asphyxia, which led to their death within 1 minute to hours after the convulsions.

The work of Harger and Hulpieu [77], mentioned above, indicates that tetramethylsuccinonitrile, like the cyanohydrins, can be fatal quite rapidly. The data in Table VI-2 indicate that the inhalation toxicity of tetramethylsuccinonitrile in rats is about 16.5 times that of acetonitrile. Because of these two considerations, NIOSH recommends that the occupational exposure limit for tetramethylsuccinonitrile not exceed a ceiling concentration of 1 ppm (6 mg/cu m) during any 15-minute period in a 10-hour workday.

NIOSH-recommended workplace environmental limits for selected nitriles are summarized in Table VI-4. This table indicates that the occupational exposure limits recommended for some nitriles are less than those recommended for hydrogen cyanide and other inorganic cyanides (4.7 ppm or 5 mg/cu m of CN as a ceiling concentration limit for any 10-minute period) [88]. This does not necessarily mean that NIOSH considers these nitriles to be more acutely toxic than hydrogen cyanide but that the toxicity information available to NIOSH on these compounds allows no better estimates to be made. However, the evidence of delayed or chronic effects from exposure of experimental animals to certain nitriles [26,48,49,56,62] suggests that prolonged exposure to at least some of these compounds may actually be more hazardous than prolonged exposure to hydrogen cyanide or an inorganic cyanide.

TABLE VI-4

NIOSH-RECOMMENDED WORKPLACE ENVIRONMENTAL LIMITS FOR SELECTED NITRILES

Nitrile	ppm	mg/cu m	Type of Limit
Acetonitrile	20	34	TWA
Propionitrile	6	14	"
n-Butyronitrile	8	22	"
Isobutyronitrile	8	22	"
Acetone cyanohydrin	1	4	Ceiling
Glycolonitrile	2	5	"
Malononitrile	3	8	TWA
Adiponitrile	4	18	"
Succinonitrile	6	20	"
Tetramethyl-succinonitrile	1	6	Ceiling

Because nitriles release cyanide in vivo [16,53-55,63,74,75] and because major signs and symptoms of acute toxicity of nitriles are attributed to the release of cyanide, exposure to several of them may produce additive effects, even at or below the recommended workplace air concentration limits. These additive effects must be considered when simultaneous exposure to two or more nitriles or other cyano compounds may occur. The following formula (from 29 CFR 1910.1000) is to be used to calculate the equivalent exposure (E_m) when such simultaneous exposure occurs:

$$E_m = C_1/L_1 + \ldots + C_n/L_n$$

where:

C_1 = the concentration of a particular substance
L_1 = the permissible exposure limit for that substance
E_m must be no greater than 1.

This formula cannot be applied to mixtures of nitriles with widely differing reactivities. The three substances in Table VI-4 for which ceiling concentration limits are recommended produce effects after brief exposure, whereas the other selected nitriles produce effects after more prolonged exposure. Where nitriles or other cyano compounds with widely different rates of toxic action occur in a mixture, the substances with the recommended TWA concentration limits and those with ceiling concentration limits may be entered into independent evaluations of equivalent exposure. The recommended limit for the mixed occupational exposure is exceeded when the E_m for either the nitriles with the recommended TWA concentration limits or those with ceiling concentration limits is greater than 1.

(b) Sampling and Analysis

Validated techniques are currently available to sample and analyze acetonitrile and tetramethylsuccinonitrile at the recommended environmental concentration limits. As discussed in Chapter IV and presented in greater detail in Appendix I, a charcoal tube method is recommended for personal breathing zone sampling of these two airborne nitriles and gas-liquid chromatography is recommended for analyzing them. These methods were selected because they have been shown to be sensitive, reproducible, and commercially available. The proposed methods allow for separation, detection, and quantitative determination of nitriles in the presence of other materials that could be encountered during their manufacture and use. Although the same general method may apply to the related mononitriles and dinitriles, until accurate methods have been validated, no sampling and analytical techniques for the eight remaining nitriles can be recommended.

(c) Medical Surveillance and Recordkeeping

Several human [2,16,26-29,33,34,38,40,80] and animal [22,23,49,53,54, 63-65,122] studies indicate that exposure to the vapor, aerosol, or liquid forms of these compounds produced skin, eye, and respiratory irritation; CNS disorders; systemic damage in various organs including the liver, kidneys, lungs, and heart; and death. Thus, a medical surveillance program should include preplacement and periodic medical examinations that focus attention on the nervous system, skin, lungs, and circulatory system. Because of the severity of possible acute effects, emergency medical attention should be provided for employees accidentally exposed to any nitrile included in this recommended standard. The therapeutic use of sodium nitrite and sodium thiosulfate for cyanide poisoning has been widely studied. Both agents increased the rate of detoxification of free cyanide ions, the former by increasing the amount of methemoglobin (a compound that avidly binds cyanide) and the latter by increasing the rate of enzymatic conversion of cyanide to thiocyanate. All medical and other pertinent records involving exposure to these nitriles should be kept for 30 years after employment ends to allow enough time for future detection of chronic sequelae that may be related to occupational exposure.

(d) Personal Protective Equipment and Clothing

Dermal [2,10,36,40] and ocular [68] contact with the liquid form or solutions of the nitriles included in the recommended standard may cause irritation of the skin and eyes in humans and animals. Zeller et al [10] reported seven cases of skin exposure to adiponitrile. One worker, whose shoe was soaked, suffered severe blistering and necrosis of the skin of the foot, which left him incapacitated for 117 days. The six remaining workers suffered minor skin irritation and inflammation that appeared 5-15 minutes after contact. Therefore, care should be exercised to ensure adequate protection against direct contact with liquid nitriles. Personal protective clothing, including eye protective devices and work clothes and shoes that prevent penetration of the nitriles, should be available and worn where exposure to these nitriles is likely [4]. Contaminated shoes and clothing should be removed immediately to prevent skin absorption. Any contaminated cloth or leather that cannot be adequately cleaned should be destroyed or discarded to prevent reuse. Work practices that prevent skin and eye contact with liquid nitriles should be followed. Emergency showers and eyewash fountains should be available for immediate use if accidental contact occurs.

Respirators may be needed by employees engaged in maintenance or repair operations that require opening of systems. Whenever respirators are provided, the employer should maintain an adequate respirator training and fitting program in accordance with 29 CFR 1910.134. In addition, a quantitative fit test of facepiece leakage is recommended because it provides a numerical index of respirator fit, does not rely solely on the

subjective response of the wearer, and therefore provides a more reliable means of protection than does qualitative fitting.

(e) Informing Employees of Hazards

At the beginning of employment, all employees should be informed of the hazards from exposure to these nitriles. Brochures and pamphlets can be effective as aids in informing employees of hazards. In addition, appropriate signs warning of the danger of exposure should be posted in any work area where there is a possibility of workplace exposure to these compounds.

A continuing education program is an important part of a preventive hygiene program for employees exposed in the workplace to hazardous materials such as mononitriles, cyanohydrins, and dinitriles. An education program, which includes training in the use of protective equipment, emergency procedures, first aid, and information about the advantages of medical examination, should be available to the employees. Trained persons should periodically apprise employees of possible sources of nitrile exposure, the potential adverse health effects associated with such exposure, the engineering controls and work practices in use to limit exposure, including those being planned, and the environmental and medical monitoring procedures used to check control procedures and the health status of employees. Personnel exposed to any of these nitriles should be warned of the potential adverse effects of accidental exposure and should be informed of the signs and symptoms of overexposure. Employees should be warned that the onset of these signs and symptoms may be delayed, particularly with exposures to mononitriles, and that their odor may not be detected.

(f) Work Practices

Processes should be designed and operated to minimize leaks of hazardous substances and to prevent spills during material handling, transfer, storage, and sampling. In addition, work practices for both routine operations and emergencies should be developed to ensure that direct contact with nitriles is avoided. When contact of liquid nitriles with the skin occurs, the affected area should be washed thoroughly with water and soap. When liquid nitriles or solutions containing nitriles are splashed into the eyes, they should be immediately flushed with a large amount of water (under low pressure). Medical attention should be promptly sought.

(g) Engineering Controls

The employer should use engineering controls and administrative procedures whenever possible to control exposures to airborne nitriles within the recommended environmental concentration limits. A closed system

of control is recommended for the nitriles included in this standard. Respiratory protective devices may be used during the time required to install adequate controls and equipment, to make process changes, to perform routine maintenance operations, or to make emergency repairs. However, respirators should not be used as a substitute for engineering controls for routine operations. The employer should prepare contingency plans for nonroutine operations, process upset, cold-weather operations, and emergencies. Facilities should be evaluated on a regular basis, and appropriate equipment and supplies should be available at proper locations to meet unusual conditions or emergencies. All such plans should be prepared in writing, understood by operating personnel and managers, and updated as required.

(h) Monitoring and Recordkeeping Requirements

Periodic sampling is needed to characterize each employee's exposure. This is accomplished with due consideration of environmental changes and changes in processes. Environmental, in addition to medical, records need to be retained primarily to provide a factual basis for the protection of an employee's health or for decisions related to an employee's health and legal rights. Such records need to be retained for 30 years after employment ends, and access to these records by the employer, employee, and designated representatives of the Department of Labor, and the Department of Health, Education, and Welfare is essential.

VII. RESEARCH NEEDS

(a) Epidemiologic Studies

Because no reports of epidemiologic studies on any of the 10 nitriles included in the recommended standard have been found and because very little is known concerning the health effects of long-term workplace exposure, such studies should be conducted. To the extent that there are records of environmental exposure, there should be an attempt to relate any such effects to exposures at specific concentrations. Longitudinal prospective studies of groups of workers exposed to nitriles at or below the recommended environmental limits would be useful to assess the validity of such limits. Because significant amounts of acetonitrile and possibly other nitriles are present in cigarette smoke, smoking histories should be taken into account in any epidemiologic studies of nitrile employees.

(b) Comparative Animal Toxicity Studies

As shown in the Basis for the Recommended Standard, the comparative animal toxicity data on which the environmental limits for the selected nitriles are based are minimal. In order to support or refute, and thus change, the environmental limits recommended in the standard, more complete comparative toxicity data are needed. Toxicities of the 10 compounds should be compared using the inhalation, oral, and percutaneous routes of administration in at least two species of experimental animals. The inhalation exposures should simulate probable schedules of workplace exposures as closely as possible. Animals exposed by the three routes for at least 18-20 months should be studied carefully after the exposures end to assess whether residual effects persist or appear despite withdrawal of the toxicant.

(c) Carcinogenicity, Mutagenicity, Teratogenicity, and Effects on Reproduction

Adiponitrile has been studied for mutagenicity using the Ames test [4]. A reproductive study of rats exposed to adiponitrile did not indicate any decreases in fertility, gestation, or viability in the first generation [78]. No report on investigations of the carcinogenic or teratogenic potential of any of the nitriles has been found. Studies, therefore, should be conducted into oncogenic and reproductive effects, preferably on mammals exposed to nitriles both by inhalation and dermally. Those nitriles most closely related to acrylonitrile in structure should be assigned the highest priority for testing.

(d) Metabolic Studies

Studies on the rate of release of cyanide ion from the various nitriles in mammalian systems should be pursued. Studies of the metabolism and detoxification of nitriles in the same animals also should be incorporated into such studies. The possibility that certain observed toxic effects of nitriles in animals may not be mediated by cyanide ions released from the nitrile should be investigated.

(e) Efficacy of Emergency Treatment

Administration of sodium nitrite and sodium thiosulfate appears to be an effective antidote for several nitriles [16,39,40]. However, this antidote has apparently not been tested for effectiveness in treating poisoning due to other nitriles. In addition, side effects from the administration of the antidote are not uncommon and, in several cases, have been severe. Therefore, research is recommended to develop effective emergency treatment less subject to risk from undesirable side effects.

(f) Biologic Monitoring

Research should be undertaken to develop and validate an improved analytical method for urinary thiocyanate for the purpose of assessing occupational exposure to nitriles. If it should prove possible to quantitate a relationship between urinary thiocyanate excretion (thiocyanate being a normal minor urinary metabolite) and exposure to nitriles, this could form the basis for biologic monitoring of nitrile exposure. The desirability of biologic monitoring as an adjunct to environmental control is emphasized by the probability that certain nitriles may be significantly absorbed through the skin [39,40,42].

(g) Sampling and Analysis

Validated methods are needed to collect and analyze eight of the selected nitriles. For the mononitriles and dinitriles, methods already available for acetonitrile and tetramethylsuccinonitrile, with appropriate modification, may be applied to the determination of n-butyronitrile, isobutyronitrile, propionitrile, adiponitrile, malononitrile, and succinonitrile. The cyanohydrins, acetone cyanohydrin and glycolonitrile, may pose a different chemical problem because of the relative ease with which they may decompose to yield cyanide and the presence of a second reactive group on the molecule. For these compounds, pH of the collection media is an important consideration, and analytical means of separation from other sources of cyanide in the same atmosphere need to be assessed. It is anticipated that work will be initiated by the Division of Physical Sciences and Engineering of NIOSH to address this requirement. Research and development of continuous monitors are also recommended.

(h) Personal Protective Equipment

Research is needed to identify or develop comfortable, lightweight materials impervious to the various nitriles for use in work clothing and personal protective equipment for workers.

(i) Combined Effects of Mixtures

In two studies [46,47] of combined toxicity of acetonitrile with other industrial chemicals, acetonitrile paired with acetone deviated most markedly from predicted additive action. Other nitriles that are used with industrial chemicals should be tested for combined effects.